



Docket No.: 22116-00005-US5
(PATENT)

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**BEFORE THE UNITED STATES BOARD OF PATENT APPEALS & INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Nicolaas M.J. Vermeulin, et al

Application No.: 09/713,512

Group Art Unit: 1621

Filed: November 14, 2000

Examiner: Peter G. O'Sullivan

For: POLYAMINE ANALOGUES AS
THERAPEUTIC AND DIAGNOSTIC AGENTS

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APPEAL BRIEF UNDER 37 CFR 1.192

Attention: Board of Patent Appeals and Interferences
Commissioner for Patents
P. O. Box 1450
Arlington, Virginia 22313-1450

Dear Sir:

This is an Appeal from the Primary Examiner's Final Rejection of Claims 30-61, 63-77
and 88-95.

I. Real Party in Interest

The real party in interest is Mediquest Therapeutics, Inc. by virtue of a name
change from Oridigm Corporation.

II. Related Appeals and Interferences

The Appeal in USSN 09/396,523 filed September 15, 1999 may directly affect or
be directly affected by or have a bearing on the Board's Decision in this Appeal.

03/28/2003 SDIRETA1 00000095 220185 09713512

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III. Status of Claims

Claims 1-95 are in the application. Claims 36-61, 63-77 and 88-95 are pending and are on Appeal. Claims 1-35, 62 and 78-87 have been cancelled.

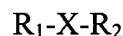
IV. Status of Amendments

No amendments to the claims have been filed after the Final Rejection.

V. Summary of Invention

The present invention relates to polyamine transport (PAT) inhibitor compounds. (See page 1, lines 11-14). Compounds of the present invention are useful for treating disorders of undesired cell proliferation, such as cancer. (See page 1, lines 14-16). Accordingly, the present invention also relates to methods of use of compounds of the present invention for such purpose.

Compounds according to the present invention are polyamine derivatives or salts represented by the formula:



wherein R_1-X- is of the formula $R-NH-CR'R''-CO-$,

wherein $-NH-CR'R''-CO-$ is a D- or L- form of valine, asparagine, or glutamine, or the D- form of lysine or arginine;

wherein R'' is H, CH_3 , CH_2CH_3 , or CHF_2 ;

wherein R is H or a head group selected from the group consisting of a straight or branched C_{1-10} aliphatic, alicyclic, single or multiring aromatic, single or multiring aryl substituted aliphatic, aliphatic-substituted single or multiring aromatic, a single or multiring heterocyclic, a single or multiring heterocyclic-substituted aliphatic and an aliphatic-substituted aromatic; and

wherein R_2 is a polyamine. (See page 12, for example, Figure 19, page 94 and

original Claim 1).

VI. Issues on Appeal

A. Claims 36-61, 63-77 and 88-95 were provisionally rejected under the judicially created doctrine of obviousness type double patenting over claims of co-pending application serial no. 09/396,523.

B. Has the Examiner established that Claims 36-41, 44-52, 60 and 61 are obvious and therefore unpatentable under 35 U.S.C. 103 (a) over the art and namely over Cherksey, et al., WO 91/00853?

VII. Grouping of Claims

For each rejection, the involved claims stand or fall together.

VIII. Argument

A. Claims 36-61, 63-77 and 88-95 are provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over the claims of application S.N. 09/396,523. The provisional rejection of claims 36-61, 63-77 and 88-95 under the judicially created doctrine of obviousness type double patenting as being unpatentable over the claims of copending application S.N. 09/396,523 will be overcome by the filing of a terminal disclaimer. Such will be filed upon overcoming the remaining rejections in the case. The filing of a terminal disclaimer is not to be construed as an admission, estoppel or acquiescence. See *Quad Environmental Technology v. Union Sanitary District*, 20 USPQ2d 1392 (Fed. Cir. 1991) and *Ortho Pharmaceuticals Corp. v. Smith*, 22 USPQ2d 1119 (Fed. Cir. 1992).

B. Cherksey Fails to Render Obvious Claims 36-41, 44-52, 60 and 61.

The rejection of claims 36-41, 44-52, 60 and 61 under 35 USC 103(a) as being unpatentable over Cherksey (WO 91/00853) is not deemed tenable. Cherksey does not render

obvious claims 36-41, 44-52, 60 and 61 since, among other things, Cherksey does not disclose the claimed stereoisomeric form of the claimed compounds, and does not lead one skilled in the art to select the claimed stereoisomers as possessing the beneficial results. As recognized and appreciated by the Examiner, applicants have provided a showing of beneficial results for the claimed stereoisomers (see page 3, lines 3 and 4 of the Office Action). For instance, as indicated in the attached Declaration of Dr. Reitha Weeks ("Weeks Declaration"), previously submitted, the D-form of lysylspermine showed unexpected differences in tissue accumulation in comparison to the L-form of lysylspermine. In particular, the tissue concentrations of the L- and D- forms of lysylspermine when measured from mouse, liver, kidney and heart tissues, are significantly different after 13 days. (Weeks Declaration, paragraphs 6 and 7). Specifically, the concentrations of the D- form were unexpectedly higher than that of the L-form. The higher tissue concentration of the D- form of lysylspermine has significance for the use of the compound in the inhibition of polyamine transport and/or the inhibition of cell proliferation. Higher tissue concentrations permit the use of lower amounts of a compound to achieve the same biological effect, such as polyamine transport inhibition and/or inhibition of cell proliferation, in a tissue.

However, the rejection of claims 36-41, 44-52, 60 and 61 was maintained based upon the incorrect premise that "it is expected that there will be differences in activity of various stereoisomers in biological systems", and the reliance upon *In re Adamson*, 125 USPQ 233 and *In re May*, 197 USPQ 601.

Even if the above conclusory statement were accurate, which it is not, the claims are still patentable since the cited art does not suggest which of the stereoisomers would possess the better properties. The statement is merely an invitation to experiment. Accordingly, the rejection is in the nature of the impermissible standard of "ought to be tried". See *Jones v. Hardy*, 220 USPQ 1021 (Fed. Cir. 1984).

The degree of differential activity exhibited by stereoisomers of biological molecules is extremely variable and must be determined empirically. In fact, many enzymes will show marked stereospecificity for one class of inhibitors, while not distinguishing between enantiomers of another class. For example, the four stereoisomers of alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid, all bind and inhibit carboxypeptidase A with similar inhibition constants. Chung *et al.*,

J. Org. Chem. 66:6462-71 (2001) (Exhibit 1, previously submitted). However, the D-configuration of another carboxypeptidase A inhibitor, N-Hydroxyaminocarbonyl)phenylalanine, binds the enzyme three times tighter than the corresponding L-configuration. Chung and Kim, *Bioorg. Med. Chem.* 9: 185-9 (2001) (Exhibit 2, previously submitted). Generally, it has been suggested that inhibitors of an enzyme's ground state may show marked stereospecificity, where irreversible and mechanism based inhibitors may show little or no stereospecificity. Kim, D.H., *Mini Rev. Med. Chem.* 1:155-61 (2001) (Exhibit 3, previously submitted). Accordingly, the potential degree of stereospecificity that may be demonstrated by the claimed compounds cannot be predicted.

The cases relied upon by the Examiner do not suggest otherwise. For instance, *In re May* found the claims rejected under 35 USC 103 to be patentable. Only the claims that were anticipated stood the test of unpatentability under 35 USC 102.

The earlier case relied upon, *In re Adamson*, involved a rejection based on a combination of at least two references. If anything it is at odds with *In re May*, as well as with *In re Williams*, 80 USPQ 150 which was cited with approval in *In re May*. In *Williams*, the Court stated that the novelty of an optical isomer is not negated by prior art disclosure of the racemate.

Furthermore, *In re Adamson* differs from the present situation. In particular, the facts of Adamson involved differences in the same activity between the L- and O- forms of a compound. In the present case, differences in a different activity (tissue accumulation) as well as an additional activity (polyamine transport inhibition) have been shown.

Also, the rejection fails to take into account more recent case law concerning 35 USC 103 as enunciated by the Federal Circuit.

Also see *In re Nathan*, 140 USPQ 601 (CCPA 1964) and *In re Magerlein*, 145 USQP 683 (CCPA 1965) which, although involving a different issue, illustrate the patentability of claims directed to specific stereoisomers of a prior art compound.

The rejection is also inconsistent with the plethora of issued patents directed to specific stereoisomers of prior art compounds.

Also, the mere fact that cited art may be modified in the manner suggested by the Examiner does not make this modification obvious, unless the cited art suggest the desirability of the modification. No such suggestion appears in the cited art in this matter. The Examiner's attention is kindly directed to *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), *In re Dembiczak et al.*

50 USPQ2d. 1614 (Fed. Cir. 1999), *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984), *In re Laskowski*, 10 USPQ2d. 1397 (Fed. Cir. 1989) and *In re Fritch*, 23, USPQ2d. 1780 (Fed. Cir. 1992).

In *Dembiczak et al.*, supra, the Court at 1617 stated: “Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., *C.R. Bard, Inc., v. M3 Sys., Inc.*, 157 F.3d. 1340, 1352, 48 USPQ2d. 1225, 1232 (Fed. Cir. 1998) (describing ‘teaching or suggestion motivation [to combine]’ as in ‘essential evidentiary component of an obviousness holding’), *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d. 1453, 1459 (Fed. Cir. 1998) (‘the Board must identify specifically...the reasons one of ordinary skill in the art would have been motivated to select the references and combine them’);...”.

Also, the cited art lacks the necessary direction or incentive to those of ordinary skill in the art to render a rejection under 35 USC 103 sustainable. The cited art fails to provide the degree of predictability of success of achieving the properties attainable by the present invention needed to sustain a rejection under 35 USC 103. See *Diversitech Corp. v. Century Steps, Inc.* 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 185 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, the properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 USC 103. See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d. 1923 (Fed. Cir. 1990), *In re Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Papesch*, supra, *In re Burt et al*, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964), and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

In view of the above conclusions, it is abundantly clear that the Primary Examiner has erred in the rejection of the claims. Accordingly, it is requested that the Board reverse the Examiner’s decision and allow the rejected claims.

The Commissioner is hereby authorized to charge any fees or credit any overpayment associated with this communication including any extension fees to Deposit Account No. 22-0185.

Dated: May 22, 2003
8008_1

Respectfully submitted,

By 

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APPENDIX 1

Claims on Appeal

36. A polyamine derivative, or salt thereof, wherein said derivative has the formula R_1-X-R_2 ,

wherein R_1-X is of the formula $R-NH-CR'R''-CO-$,

wherein $-NH-CR'R''-CO-$ is a D- or L- form of valine, asparagine, or glutamine, or the D- form of lysine or arginine;

wherein R'' is H, CH_3 , CH_2CH_3 , or CHF_2 ;

wherein R is H or a head group selected from the group consisting of a straight or branched C_{1-10} aliphatic, alicyclic, single or multiring aromatic, single or multiring aryl substituted aliphatic, aliphatic-substituted single or multiring aromatic, a single or multiring heterocyclic, a single or multiring heterocyclic-substituted aliphatic and an aliphatic-substituted aromatic; and

wherein R_2 is a polyamine.

37. The derivative of claim 36 wherein R is H.

38. The derivative of claim 37 wherein $-NH-CR'R''-CO-$ is the D- form of lysine.

39. The derivative of claim 38 wherein R_2 is spermine.

40. The derivative of claim 39 wherein R_1-X is attached to spermine at the N_1 position of spermine.

41. A composition comprising a polyamine derivative or salt according to any one of claims 36-39 and one or more pharmaceutically acceptable excipients.

42. The composition of claim 41 further comprising a polyamine synthesis inhibitor.

43. The composition of claim 42 wherein said inhibitor is difluoromethylornithine (DFMO).

44. The composition of claim 41 wherein said one or more pharmaceutical excipients are suitable for treating a disease or condition in which the inhibition of polyamine transport is desirable.

45. The composition of claim 41 further comprising one or more auxiliary agents or one or more liquid carriers.

46. The composition of claim 45 comprising a preservative or a stabilizer or both as said auxiliary agent.

47. The composition of claim 46 comprising a stabilizer as an auxiliary agent.

48. The composition of claim 45 comprising peanut oil or olive oil as said liquid carrier.

49. The composition of claim 45 further comprising water.

50. The composition of claim 41 formulated as a solid.

51. The composition of claim 50 formulated as a capsule, impregnated wafer, tablet or powder.

52. A method comprising contacting a cell with a polyamine derivative or salt according to any one of claims 36-39.

53. The method of claim 52 wherein polyamine transport in said cell is inhibited.

54. The method of claim 52 wherein said cell is in a subject with a disease or condition associated with undesired cell proliferation.

55. The method of claim 54 wherein said undesired cell proliferation is associated with proliferation of cells of the immune system, cells of the vascular neointima, tumor cells, or with undesired angiogenesis.

56. The method of claim 55 wherein said disease or condition is cancer or post-angioplasty injury.

57. The method of claim 54 wherein said contacting is administration of said polyamine derivative or salt to said subject systemically or topically.

58. The method of claim 54 wherein said contacting is administration of said polyamine derivative or salt to said subject orally, parenterally, transdermally, intravaginally, intranasally, intrabronchially, intracranially, intraocularly, intraaurally, rectally, by infusion, or by injection.

59. The method of claim 58 wherein said administration by injectin is intravenous, subcutaneous, intramuscular, intracranial, or intraperitoneal.

60. A method comprising contacting a cell with a polyamine derivative or salt thereof, wherein said derivative has the formula R_1-X-R_2 ,

wherein R_1-X- is of the formula $R-NH-CR'R''-CO-$,

wherein $-NH-CR'R''-CO-$ is the L- form of lysine or arginine;

wherein R'' is H, CH_3 , CH_2CH_3 , or CHF_2 ;

wherein R is H or a head group selected from the group consisting of a straight or branched C_{1-10} aliphatic, alicyclic, single or multiring aromatic, single or multiring aryl substituted aliphatic, aliphatic-substituted single or multiring aromatic, a single or multiring heterocyclic, a single or multiring heterocyclic-substituted aliphatic and an aliphatic-substituted aromatic; and R_2 is a polyamine

under conditions such that polyamine transport in said cell is inhibited.

61. The method of claim 60 wherein R'' and R are H; R_2 is spermine; and R_1-X- is attached to R_2 at the N_1 position of spermine.

63. The method of claim 60 or 61 wherein said cell is in a subject with a disease or condition associated with undesired cell proliferation.

64. The method of claim 63 wherein said undesired cell proliferation is associated with proliferation of cells of the immune system, cells of the vascular neontima, tumor cells, or with undesired angiogenesis.

65. The method of claim 64 wherein said disease or condition is cancer or post-angioplasty injury.

66. The method of claim 63 wherein said contacting is administration of said polyamine derivative or salt to said subject systemically or topically.

67. The method of claim 63 wherein said contacting is administration of said polyamine derivative or salt to said subject orally, parenterally, transdermally, intravaginally, intranasally, intrabronchially, intracranially, intraocularly, intraaurally, rectally, by infusion, or by injection.

68. The method of claim 67 wherein said administration by injection is intravenous, subcutaneous, intramuscular, intracranial, or intraperitoneal.

69. A method comprising contacting a cell with a polyamine derivative or salt according to any one of claims 36-39 and a polyamine synthesis inhibitor.

70. The method of claim 69 wherein said inhibitor is DFMO.

71. The method of claim 69 wherein polyamine transport in said cell is inhibited.

72. The method of claim 69 wherein said cell is in a subject with a disease or condition associated with undesired cell proliferation.

73. The method of claim 72 wherein said undesired cell proliferation is associated with proliferation of cells of the immune system, cells of the vascular neointima, tumor cells, or with undesired angiogenesis.

74. The method of claim 73 wherein said disease or condition is cancer or post-angioplasty injury.

75. The method of claim 72 wherein said contacting is administration of said polyamine derivative or salt to said subject systemically or topically.

76. The method of claim 72 wherein said contacting is administration of said polyamine derivative or salt to said subject orally, parenterally, transdermally, intravaginally, intranasally, intrabronchially, intracranially, intraocularly, intraaurally, rectally, by infusion, or by injection.

88. The method of claim 60 or 61, wherein said contacting further comprises contacting said cell with a polyamine synthesis inhibitor.

89. The method of claim 88, wherein said polyamine synthesis inhibitor is α -difluoromethylornithine.

90. The method of claim 88 wherein said cell is in a subject with a disease or condition associated with undesired cell proliferation.

91. The method of claim 89 wherein said cell is in a subject with a disease or condition associated with undesired cell proliferation.

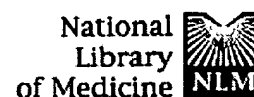
92. The method of claim 90 wherein said undesired cell proliferation is associated with cancer.

93. The method of claim 91 wherein said undesired cell proliferation is associated with cancer.

94. The method of claim 54 wherein said undesired cell proliferation is associated with cancer.

95. The method of claim 63 wherein said undesired cell proliferation is associated with cancer.

EXHIBIT 1



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1: J Org Chem 2001 Sep 21;66(19):6462-71

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**Mechanistic insight into the inactivation of carboxypeptidase A by alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid, a novel type of irreversible inhibitor for carboxypeptidase A with no stereospecificity.****Chung SJ, Chung S, Lee HS, Kim EJ, Oh KS, Choi HS, Kim KS, Kim YJ, Hahn JH, Kim DH.**

Center for Biofunctional Molecules and Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, Korea.

On the basis of the active site topology and enzymic catalytic mechanism of carboxypeptidase A (CPA), a prototypical zinc-containing proteolytic enzyme, alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid (1), was designed as a novel type of mechanism-based inactivator of the enzyme. All four possible stereoisomers of the inhibitor were synthesized in an enantiomerically pure form starting with optically active aspartic acid, and their CPA inhibitory activities were evaluated to find that surprisingly all of the four stereoisomers inhibit CPA in a time dependent manner. The inhibited enzyme did not regain its enzymic activity upon dialysis. The inactivations were prevented by 2-benzylsuccinic acid, a competitive inhibitor that is known to bind the active site of the enzyme. These kinetic results strongly support that the inactivators attach covalently to the enzyme at the active site. The analysis of ESI mass spectral data of the inactivated CPA ascertained the conclusion from the kinetic results. The values of second-order inhibitory rate constants ($k(\text{obs})/[\text{I}](\text{o})$) fall in the range of 1.7-3.6 $\text{M}^{-1} \text{min}^{-1}$. The lack of stereospecificity shown in the inactivation led us to propose that the ring cleavage occurs by the nucleophilic attack at the 2-position rather than at the 5-position and the ring opening takes place in an addition-elimination mechanism. The tetrahedral transition state that would be generated in this pathway is thought to be stabilized by the active site zinc ion, which was supported by the PM3 semiempirical calculations. In addition, alpha-benzyl-2-oxo-1,3-oxazolidine-5-acetic acid (18), a structural isomer of 1 was also found to inactivate CPA in an irreversible manner, reinforcing the nucleophilic addition-elimination mechanism. The present study demonstrates that the transition state for the inactivation pathway

plays a critical role in determining stereochemistry of the inactivation.

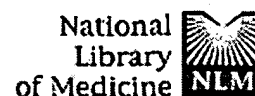
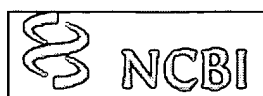
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EXHIBIT 2



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Related Articles, Links

**ELSEVIER SCIENCE
FULL-TEXT ARTICLE****N-(Hydroxyaminocarbonyl)phenylalanine: a novel class of inhibitor for carboxypeptidase A.****Chung SJ, Kim DH.**

Center for Biofunctional Molecules and Department of Chemistry, Pohang University of Science and Technology, Namgu, South Korea.

N-(Hydroxyaminocarbonyl)phenylalanine (1) was designed rationally as a new type of inhibitor for carboxypeptidase A (CPA). The designed inhibitor was readily prepared from phenylalanine benzyl ester in two steps and evaluated to find that rac-1 inhibits CPA in a competitive fashion with the K_i value of 2.09 μM . Surprisingly, inhibitor 1 having the D-configuration is more potent ($K_i = 1.54 \mu\text{M}$) than its antipode by about 3-fold. A possible explanation for the stereochemistry observed in the inhibition of CPA with 1 is presented.

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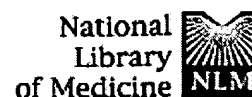
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Origin of chiral pharmacology: stereochemistry in metalloprotease inhibition.

Kim DH.

Center for Biofunctional Molecules and Department of Chemistry, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, Korea. dhkim@postech.ac.kr

The stereospecificity shown by a wide variety of inhibitors that are effective for carboxypeptidase A (CPA), a representative zinc protease is analyzed on the basis of inhibitor type. In cases of ground state analog inhibitors and transition state analog inhibitors, the stereoisomers having the stereochemistry that corresponds to stereochemistry of substrate are more potent, but in the case of irreversible inhibitors including mechanism-based inactivators the preferred inhibitory stereochemistry cannot be predicted simply from the substrate stereospecificity. The Ogston's three point fit concept may be of great value in understanding the inhibitory stereochemistry of reversible competitive inhibitors. On the other hand, the stereochemistry of irreversible inhibitors may possibly be predicted on the ground of the transition state structure that plays a critical role in the inactivation pathway.

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- Review
- Review, Tutorial

PMID: 12369980 [PubMed - indexed for MEDLINE]

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